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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,626	09/25/2003	Xiaodong Wang	UTSD:1493	6739

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,626	WANG ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 7/9/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/28/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 7/9/2006, claims 1-4 are pending in the application and currently under examination.

Claim Objections

Claim 2 is objected to because of the following informalities: For consistency and clarity, it is suggested that the recitation "Drosophila" be italicized, as in Claim 1. Appropriate correction is required.

Response to Arguments—Claim Rejections - 35 USC § 112

Claims 1–4 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As amended, claim 1 recites a method for making siRNA *in vitro*, comprising recombinantly coexpressing a Dicer protein with a *Drosophila* R2D2 protein to form a complex comprising the R2D2 protein and the Dicer protein *in vitro*, and contacting the complex with a target double-stranded RNA comprising a predetermined sequence under conditions wherein the complex cleaves the dsRNA into siRNA *in vitro*. Claim 2 limits the method by stating that the Dicer protein is a *Drosophila* Dicer-2 protein. Claims 3 and 4 limit the methods of 1 and 2 by stating that the proteins are coexpressed in a baculovirus system.

In their remarks, Applicants state that the recited Dicer protein comprises a well known family of large non-canonical RNase III enzymes, and that Dicer proteins have been used to make siRNA. Applicants cite patent and non-patent literature in support thereof. Applicants state that the recited Drosophila R2D2 protein is a well-known, art-recognized protein for which the specification provides a GenBank Accession No. Applicants state that those skilled in the art would recognize the scope and meaning of the recited Dicer and Drosophila R2D2 proteins.

Applicants' arguments have been fully considered but are not found persuasive.

Applicants' amendments to the claims do not specifically address nor overcome the rejection for lack of written description support.

To be clear, it is the Examiner's position that adequate written description support does not exist for methods of making siRNA using any Dicer protein from any organism with any *Drosophila* R2D2 protein, because Applicants have not demonstrated that, as the effective filing date, they were in possession of the complete genus of Dicer proteins from any organism that will form siRNA-generating complexes with any *Drosophila* R2D2.

Instead, Applicants have adequately described one (1) method of making siRNA: comprising combining recombinantly expressed *Drosophila* R2D2 protein, encoded by GenBank Accession No. NM_135308, with *Drosophila* Dicer-2 protein, and contacting the proteins in a cell-free solution with dsRNA (see pages 6-7).

It is the Examiner's position that the family of RNase III enzymes expressed by different organisms includes many structurally and functionally distinct members, as evidenced by the prior and post-filing art of record (Bernstein et al., 2001; and Meister et al., 2004), and it is unclear in view of Applicant's specification and the state of the prior art which of these proteins will or will not function together with *Drosophila* R2D2 protein to form functionally active, siRNA-generating complexes as required by the instantly claimed invention. The fact that one of skill in the art could use routine experimentation to easily or readily identify which of the many art-recognized Dicer-like, RNase III enzymes will work in the instant invention is not a factor for consideration in this analysis, since written description is separate from enablement.

What is needed is a description of the Dicer proteins themselves. Currently, the Dicer proteins are defined only by a statement of function or result—forming heterodimers with R2D2 and cleaving dsRNA—with no distinguishing information about the identity of the claimed Dicer proteins.

Similarly, Applicants' claims encompass any *Drosophila* R2D2 protein. Adequate support for the genus of all *Drosophila* R2D2 proteins does not exist. Contrary to Applicants' statement that Drosophila R2D2 protein is a well-known, art-recognized protein for which the specification provides a GenBank Accession No., the Examiner finds no prior art reports identifying, characterizing, or exemplifying the activity of the protein encoded by GenBank

Accession No. NM_135308. Rather it appears that Applicants are the first to conceive and reduce to practice the instant method for making siRNA using protein recombinantly expressed from GenBank Accession No. NM_135308. Thus R2D2 does not represent a well known art-recognized protein, and the instant application does not enable the skilled artisan to envision all other Drosophila R2D2 proteins, if any, that function with any Dicer protein to produce siRNA.

Additionally, the statement that Dicer protein comprises a well known family of large non-canonical RNase III enzymes does little to help distinguish the non-canonical RNase III enzymes that are part of the invention. What feature or features distinguish "non-canonical" enzymes from "canonical" enzymes? What is needed to satisfy the written description requirement is a precise definition, such as by structure, formula, chemical name, or physical properties.

Currently, the recombinantly expressed proteins are recited by name only, without providing any specific identification of the particular amino acid sequence(s) to be used or cDNA sequence(s) to be expressed.

Thus, Applicants have not demonstrated that they were in possession of the full genus of methods for coexpressing any Dicer protein with any *Drosophila* R2D2 protein to make siRNA.

Therefore, adequate written description does not exist for the entire scope of the invention as now claimed, because the specification describes neither a representative number of species nor a structure/function correlation such that one of skill in the art would recognize Applicants were in possession of the genus of methods now claimed at the time the application was filed.

Reasoning and/or technical evidence in support of a finding for lack of written description of the currently claimed invention may be found in a previous Office Action.

The recitation of a SEQ ID NO: identifier corresponding to GenBank Accession No. NM_135308, described at pages 2 and 3 of the specification as corresponding to the *Drosophila* R2D2 of the invention, in the embodiment claimed in claim 2 would overcome this rejection as applied to claims 2 and 4. In view of the state of the prior art, *Drosophila* Dicer-2 protein is considered to be sufficiently well-characterized in terms of both structure and function, and one of skill would immediately recognize the distinguishing characteristics of the genus of *Drosophila* Dicer-2 proteins needed to practice the instant invention.

***

Claims 1–4 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

methods of making siRNA *in vitro* in insect cells, *Drosophila* cell lysates, or in a cell-free assay by coexpressing a *Drosophila* Dicer-2 protein and *Drosophila* R2D2 protein, encoded by GenBank Accession No. NM_135308 to form a complex and then contacting the complex with dsRNA *in vitro* in an insect cell, *Drosophila* cell lysate, or cell-free assay to form siRNA *in vitro* in an insect cell, *Drosophila* cell lysate, or cell-free assay,

does not reasonably provide enablement for:

methods of making siRNA *in vitro* in any cell, including any mammalian cell, by coexpressing any dicer protein, including any *Drosophila* Dicer-2 protein, with any *Drosophila* R2D2 protein to form a complex and then contacting the complex with dsRNA *in vitro* in any cell to form siRNA *in vitro* in any cell.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

In their broadest embodiments, the claimed methods require the recombinant coexpression and formation in any cell of a Dicer/Drosophila R2D2 protein-protein heterodimer, having siRNA-generating activity.

The instantly claimed methods require access to, knowledge of, or the ability to routinely identify without undue experimentation all Dicers from all species that bind any Drosophila R2D2 protein and that produce siRNA when bound to R2D2 in any cell or cell-free solution in vitro.

It is the Examiner's position that it would require undue experimentation to screen and identify all Dicers from all species that 1) interact with and cooperate with any Drosophila R2D2 to form a complex, and 2) produce siRNA in vitro in any cell or in any cell-free assay.

It is important to note that claim 1 encompasses methods of producing siRNA in any cell, including any mammalian cell, in vitro. To be sure, claim 1 encompasses methods of performing RNAi in any cell in vitro, wherein the method comprises recombinantly coexpressing the required proteins in the cell and contacting the cell with dsRNA of any length. Applicants have not taught one of skill how to make and use any Dicer protein/Drosophila R2D2 complex to produce siRNA in any cell in vitro. Furthermore, Applicants have not taught one of skill how to deliver recombinantly coexpressed proteins or complexes thereof into any cell in vitro for the production of siRNA in any cell in vitro, as now claimed in claims 1 and 2.

It is the examiners position that the recited genus of Dicer proteins includes countless numbers of structurally and functionally distinct proteins from virtually any species, as evidence by the art of record, and there is no reasonable starting point from which to begin the screening process aside from screening for R2D2 binding affinities and dsRNA cleaving activities.

In their remarks, Applicants state that the recited Dicer proteins comprise a well known family of large non-canonical RNase III enzymes, and that Dicer proteins have been used to make siRNA. Applicants cite patent and non-patent literature in support thereof. Applicants state that the recited Drosophila R2D2 protein is a well-known, art-recognized protein for which the specification provides a GenBank Accession No. Applicants state that those skilled in would have no trouble substituting one known Dicer protein for another in the assay, and that to

practice the claimed method the skilled artisan would need do no more than routine screening, using the recited method, to confirm the candidate protein is operative in the method.

Applicants' arguments have been fully considered but are not found persuasive.

The specification teaches working examples comprising recombinantly coexpressing Drosophila Dicer-2 with Drosophila R2D2, purifying the proteins, forming a complex, and then contacting the complex with dsRNA (pages 6-7). The specification teaches that Dicer-2 will cleave dsRNA on its own, without any added R2D2, and that R2D2 may stabilize Dicer-2 and regulate siRNA production in Drosophila cells (pages 6 and 7).

While Applicants comment in their remarks that the specification supports cell-based methods at p. 6, lines 25-31, the Examiner finds that the support cited describes the purification of the recombinantly expressed proteins using affinity chromatography. No support is found for recombinantly coexpressing the proteins in any mammalian cell and transfecting the cell with dsRNA to produce siRNA in the cell. Rather, Applicants' working examples of siRNA generation from recombinantly coexpressed dicer and R2D2 proteins are directed to cell free assays.

It is unclear how one of skill is to recognize and identify all other putative dicer proteins for use in the instant claims. The specification teaches only that dicer has an art-recognized function as having the capability of generating siRNA (page 5-6). However, the specification also teaches that many different RNase III proteins are known (page 1), and that some are capable of forming complexes with R2D2 and generating siRNA, while others are, apparently, less prone to forming complexes with R2D2 and generating siRNA (page 5, lines 25-26).

Moreover, the instant application teaches that R2D2 in fact does not affect the ability of DCR-2 to recruit or cleave dsRNA *in vitro*, but that it may stabilize DCR-2 and thereby positively regulate siRNA production in *Drosophila* cells (page 7). How, then, is one of skill to identify all putative dicer and *Drosophila* R2D2 proteins and complexes thereof having the ability to positively regulate siRNA production in *Drosophila* cells? No particular assay or detection method has been taught or suggested.

Considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims stand rejected for failing to comply with the enablement requirement.

Response to Applicants' Arguments

Applicants' arguments presented on 7/9/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
August 14, 2006